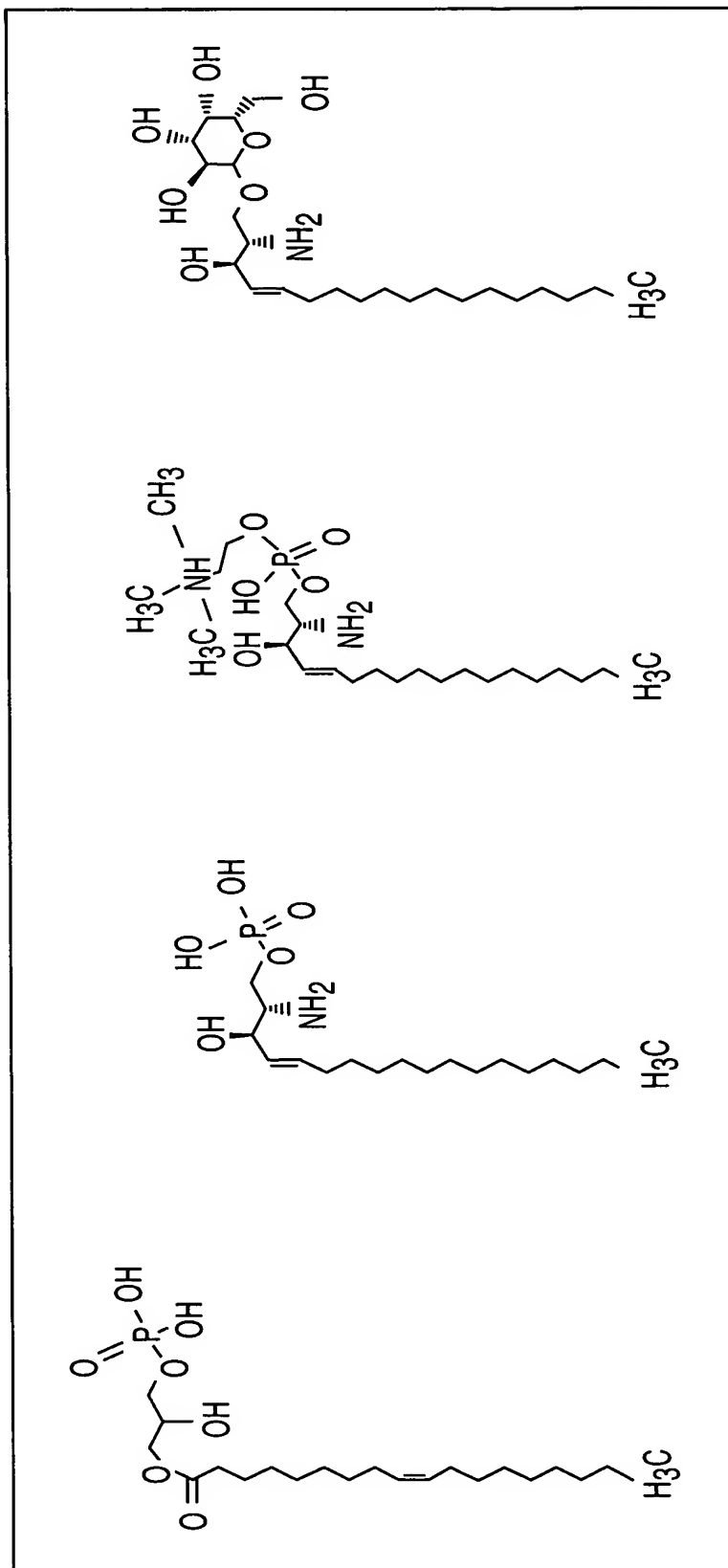Fig.1A

LPA   S1P   SPC   Psychosine
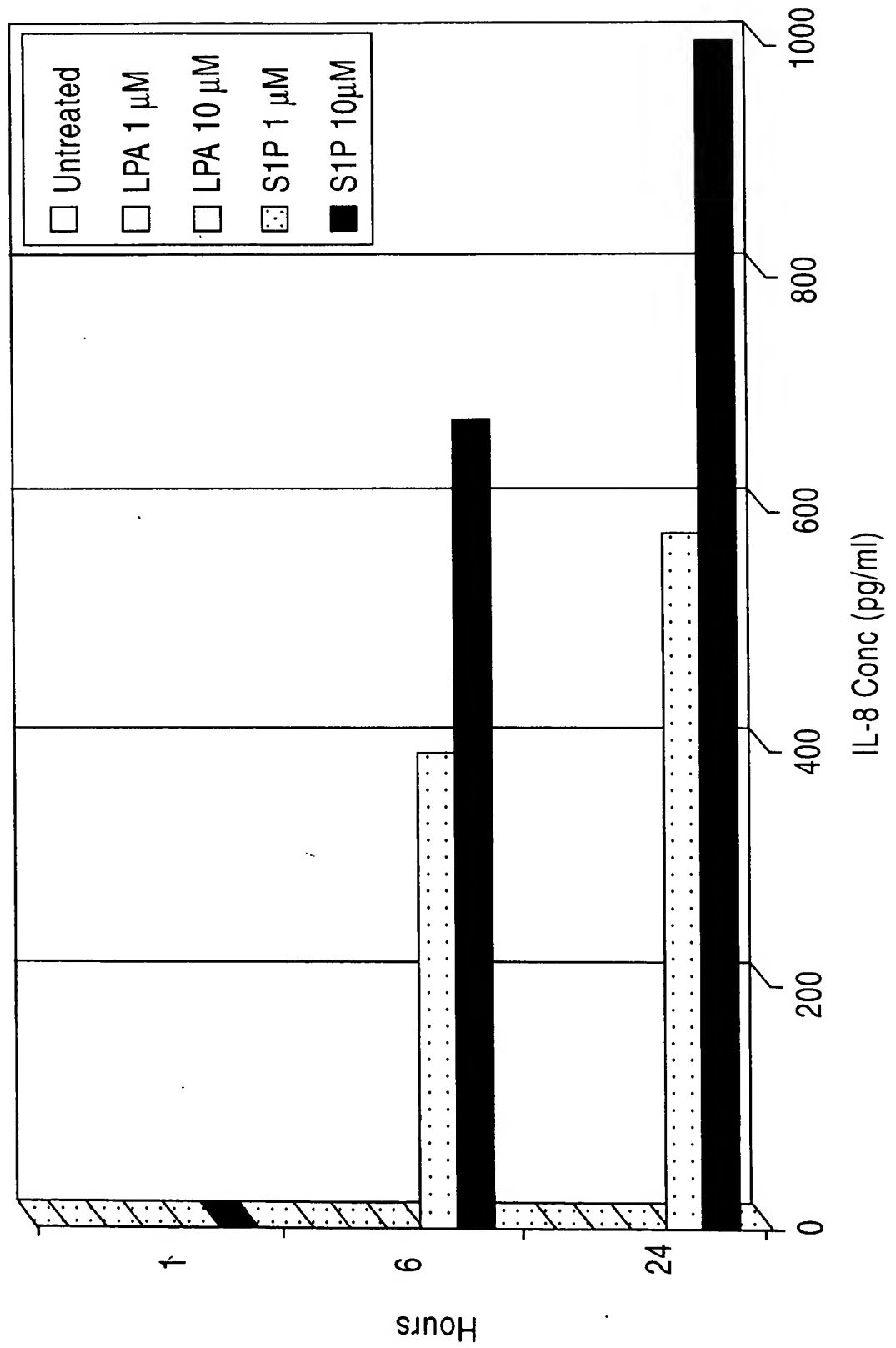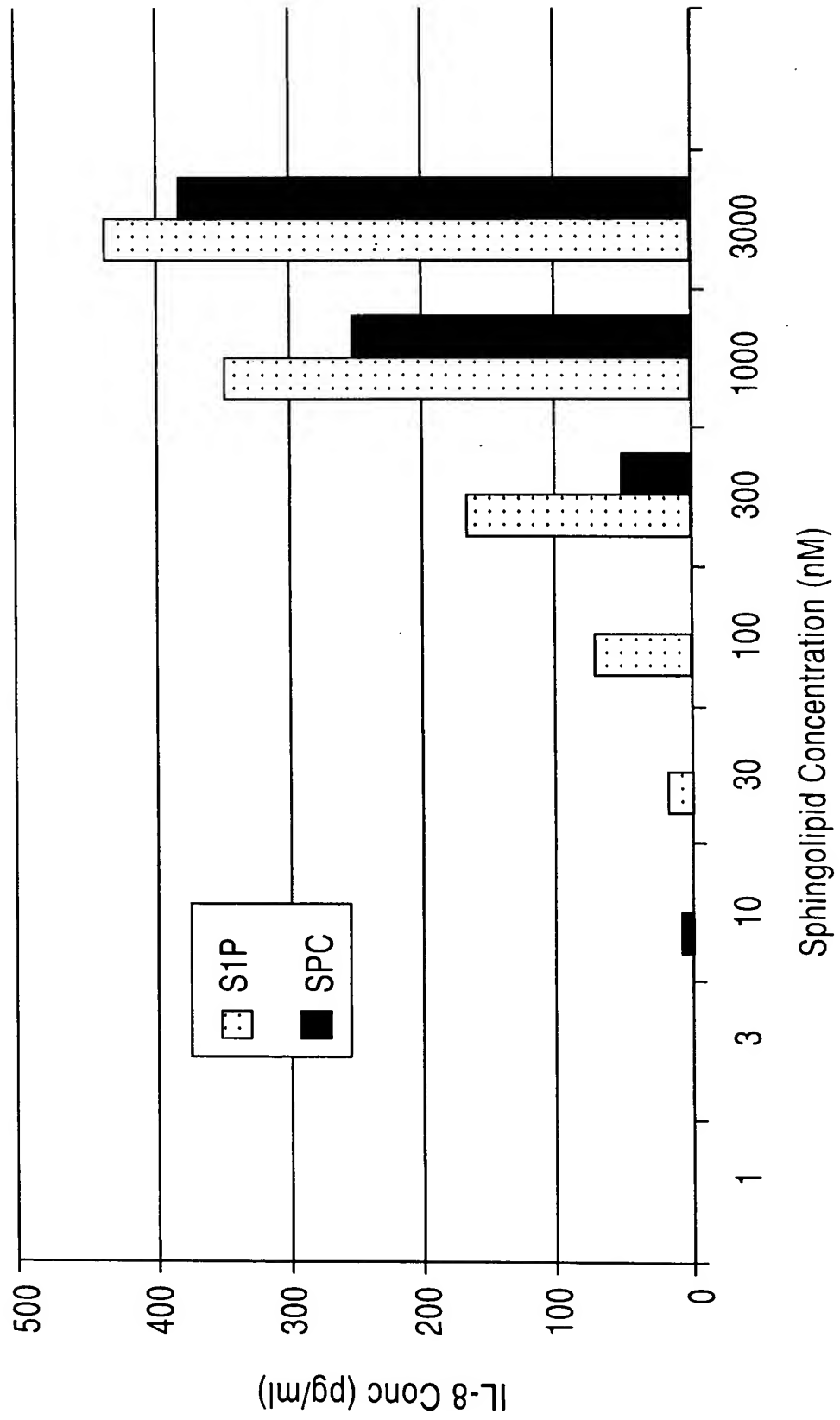
Fig.1B
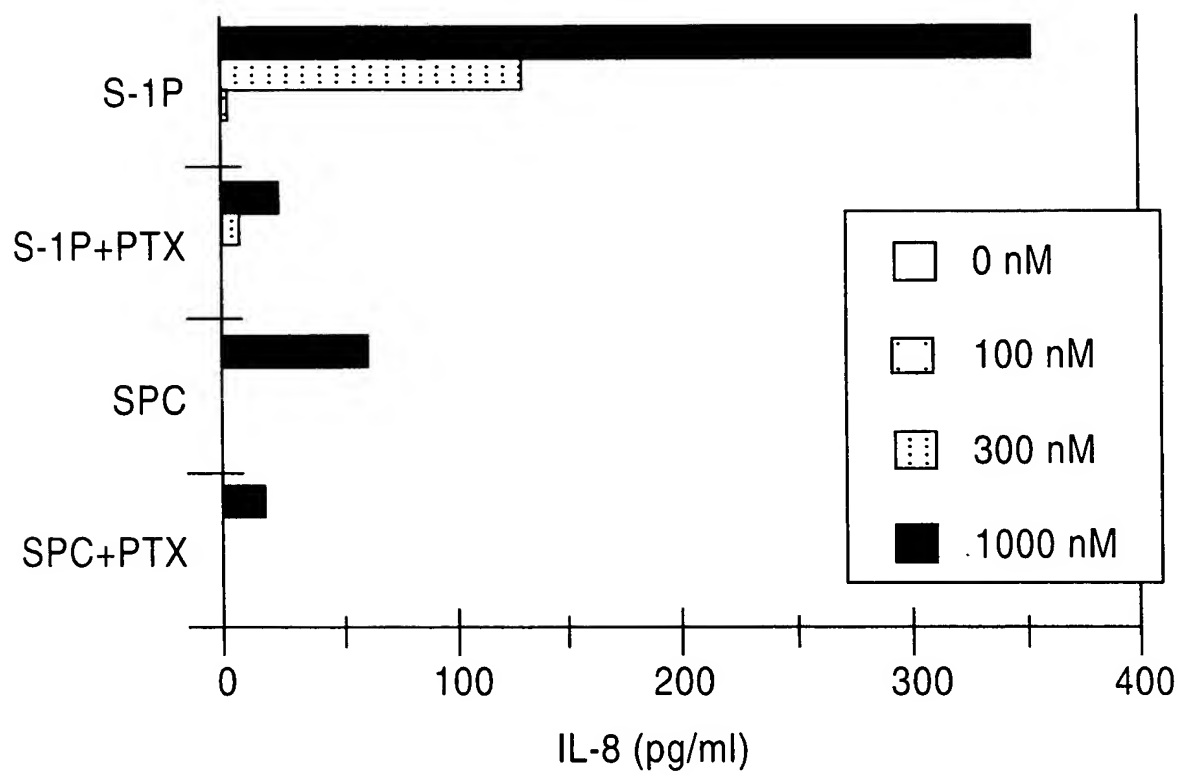
Fig.2A

Fig.2B
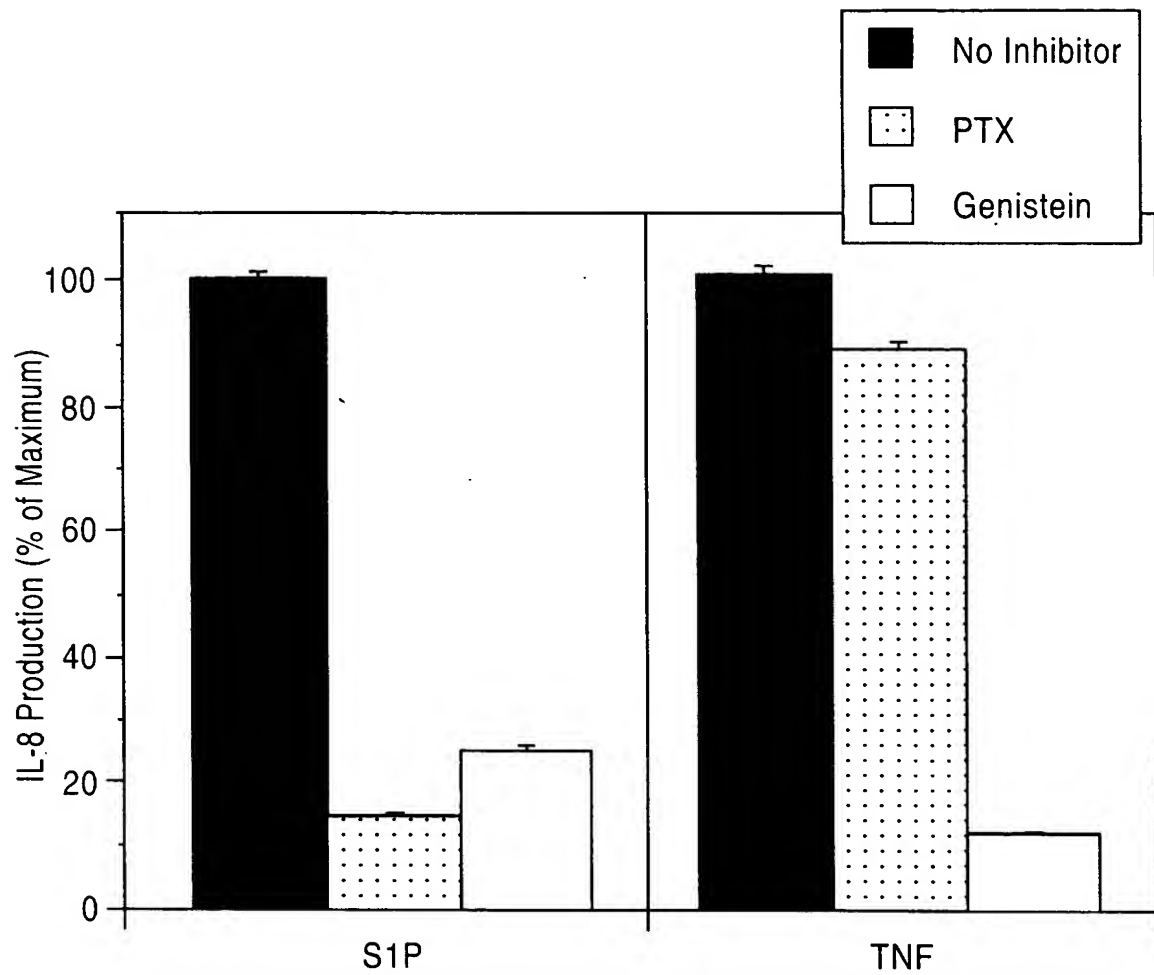
Fig.3

Fig.4A

IL-8 Conc (pg/ml)
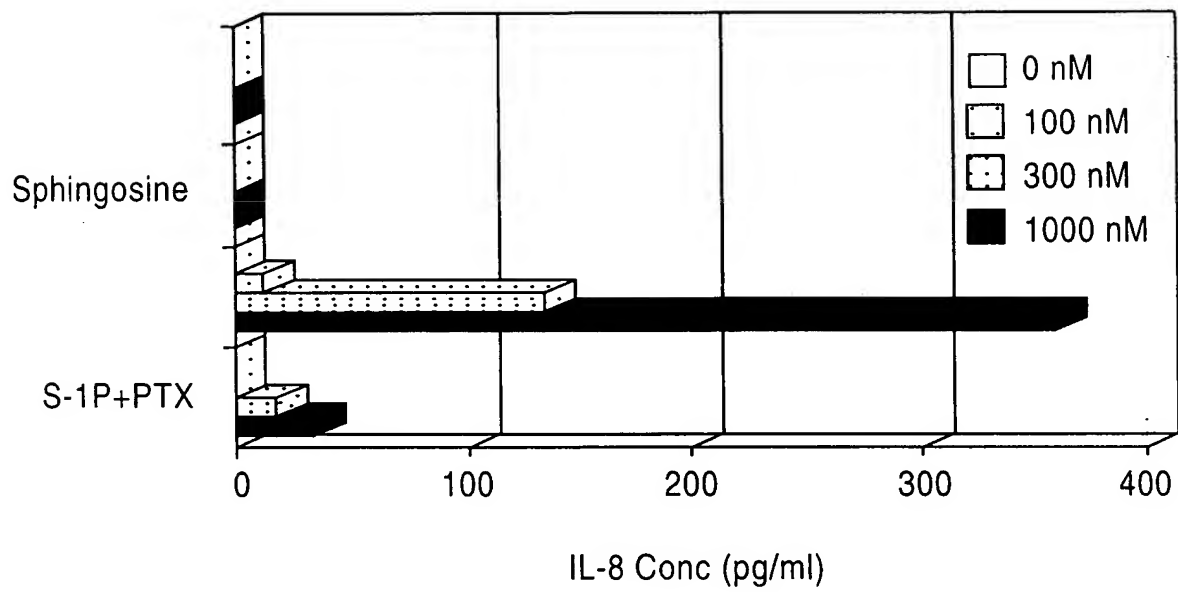
Fig.4B

Fig.5

Fig.6A

Fig.6B

Fig.7

Fig.8

IL-8 (pg/ml)

Control

S1P

S1P + 10 μM NDGA

S1P + 40 μM NDGA

S1P + 10 mM NAC

S1P + 30 mM NAC

Fig.9
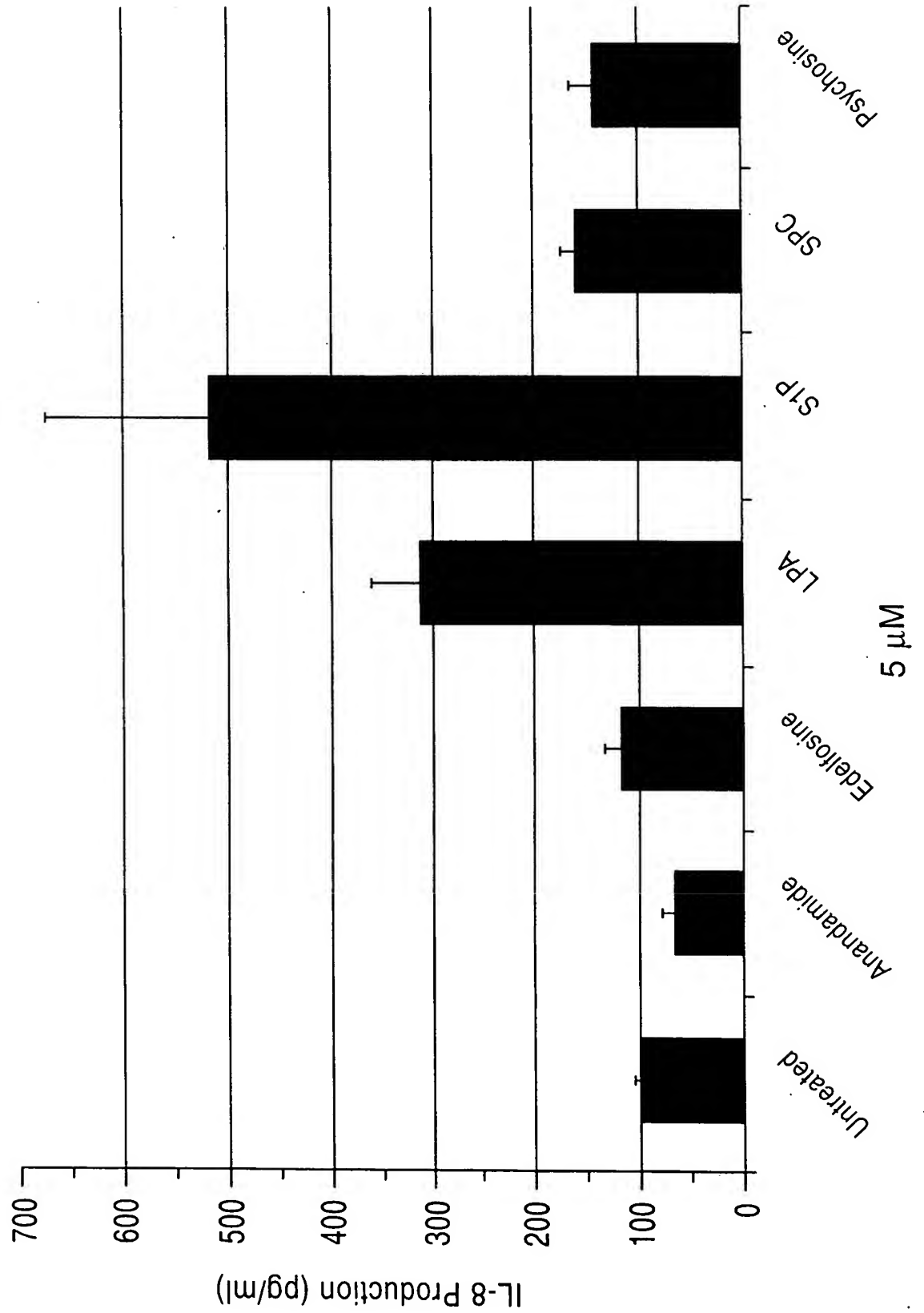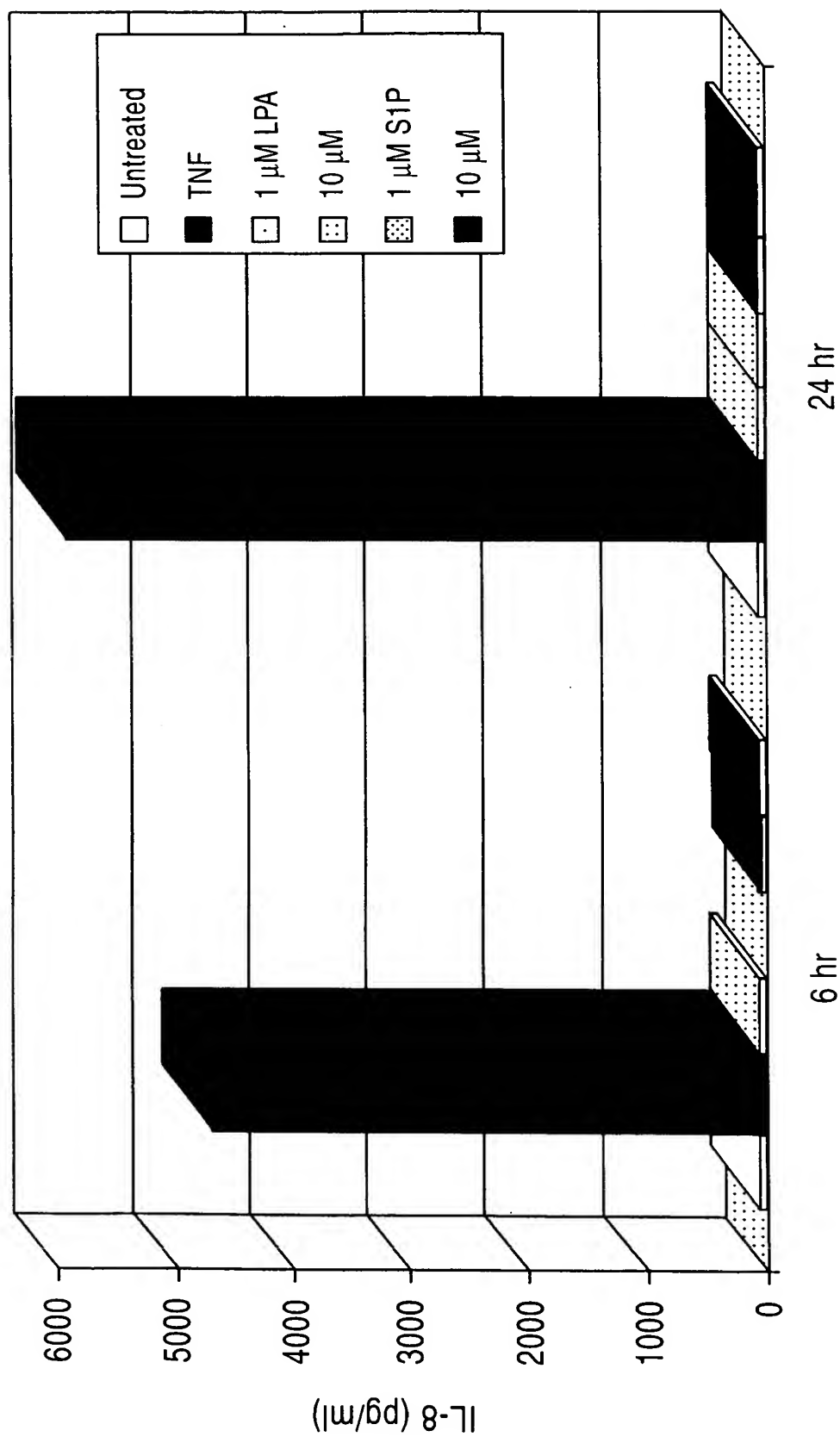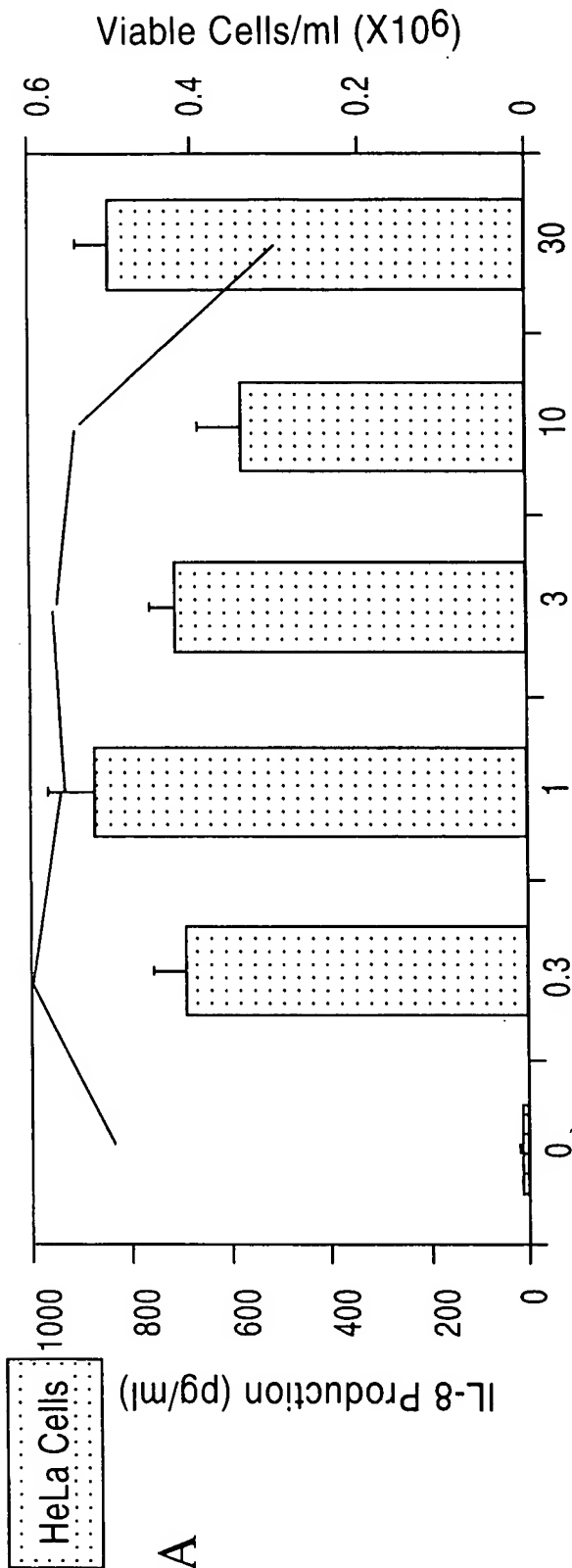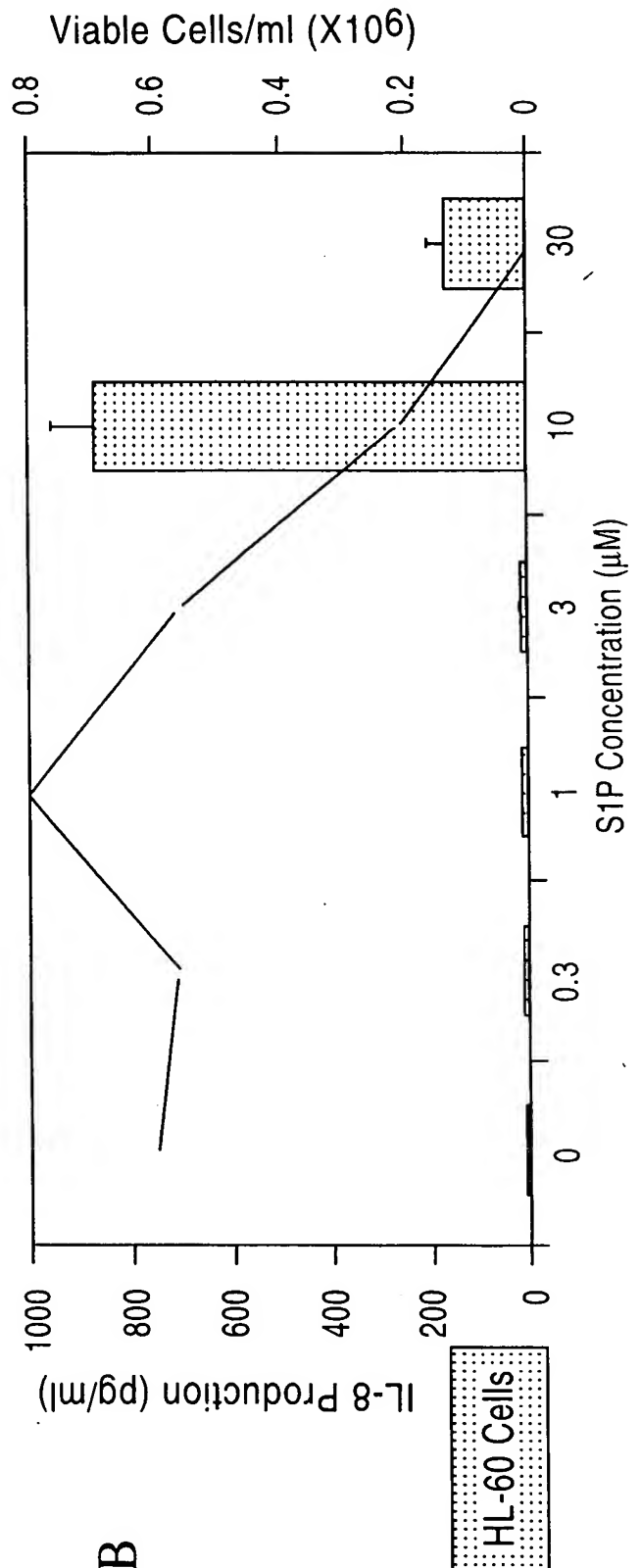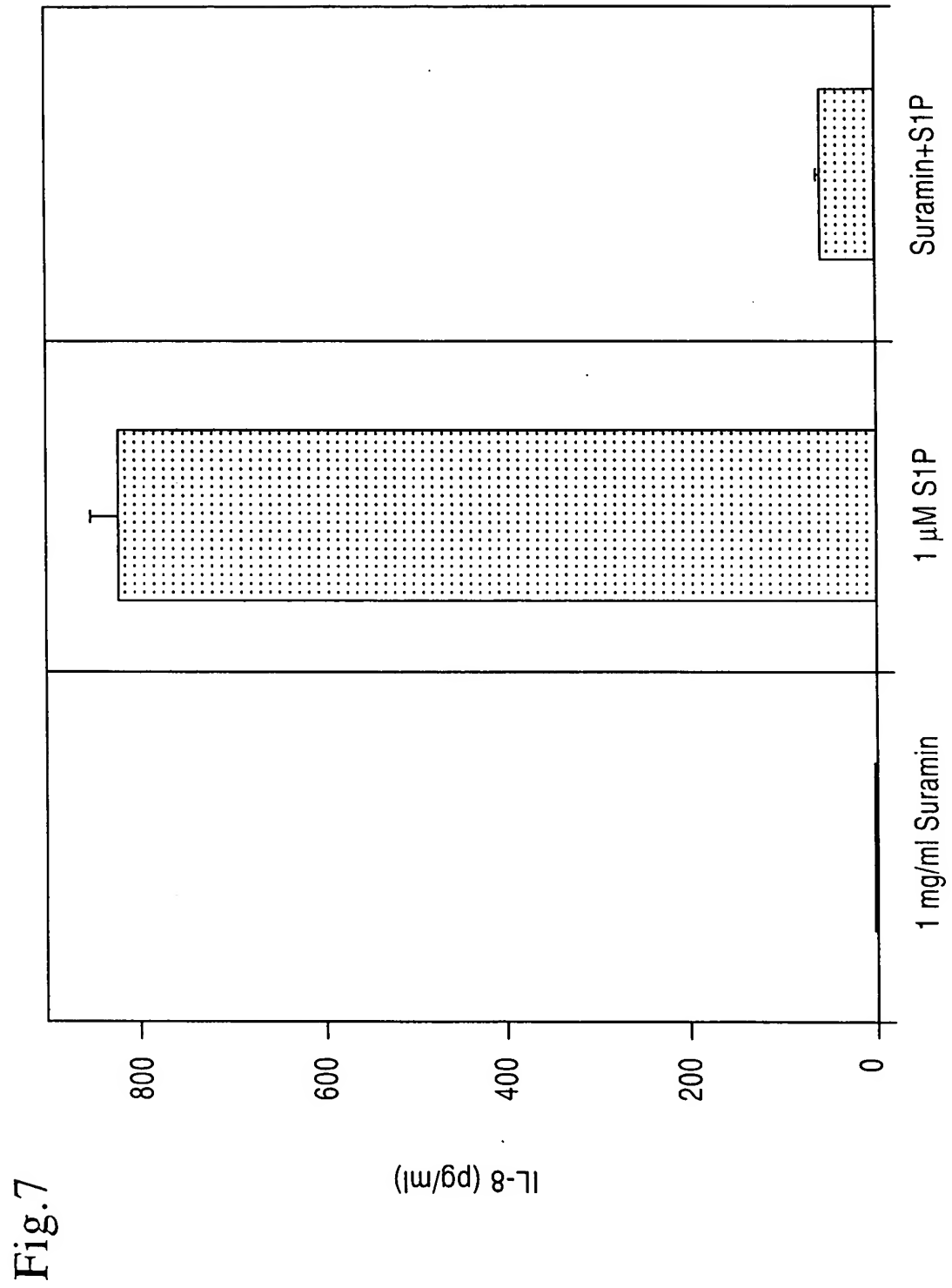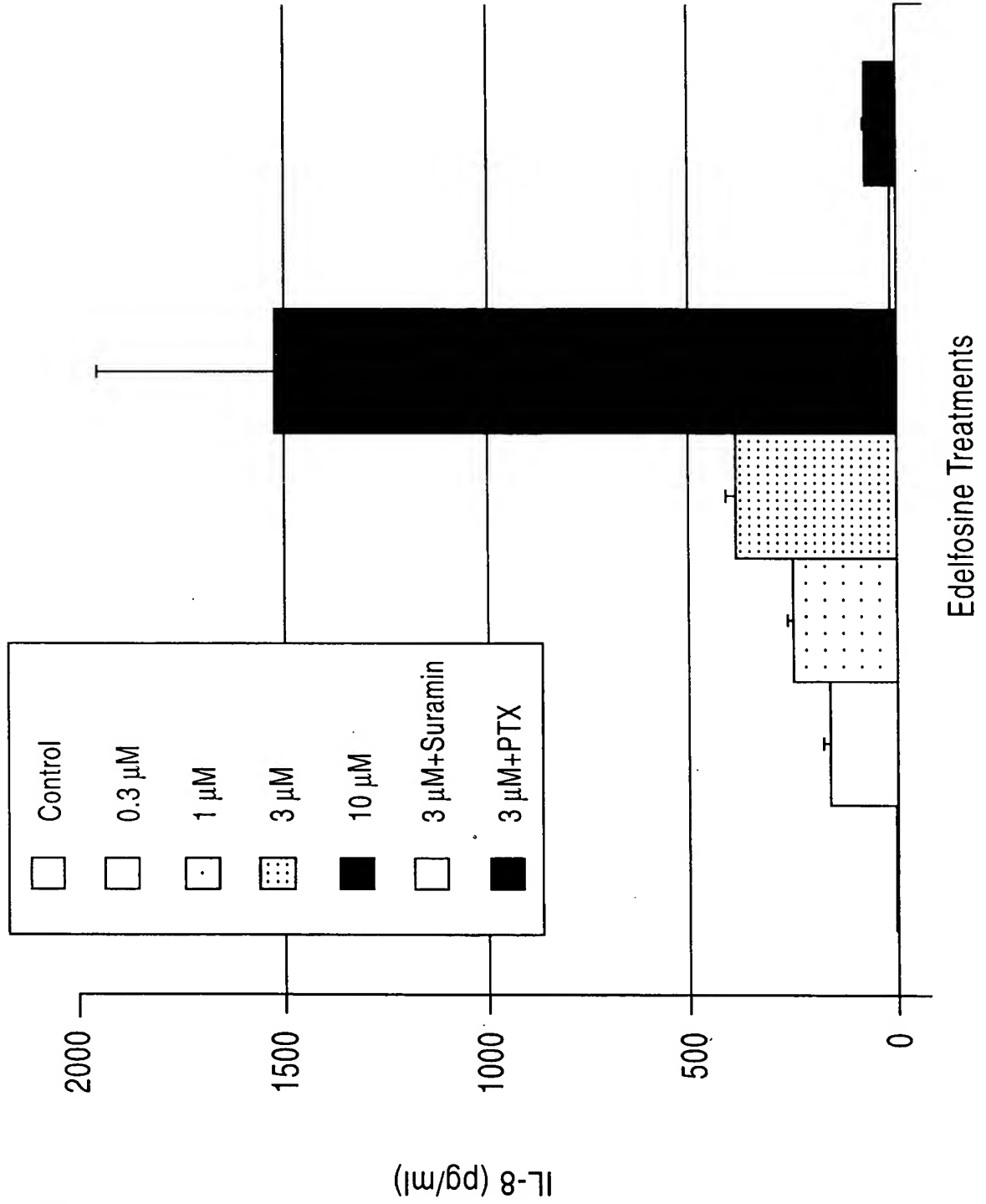
Fig.10A

Fig.10B

Fig.11B

pcDNA3

Fig.11A

Edg-4

Fig.12
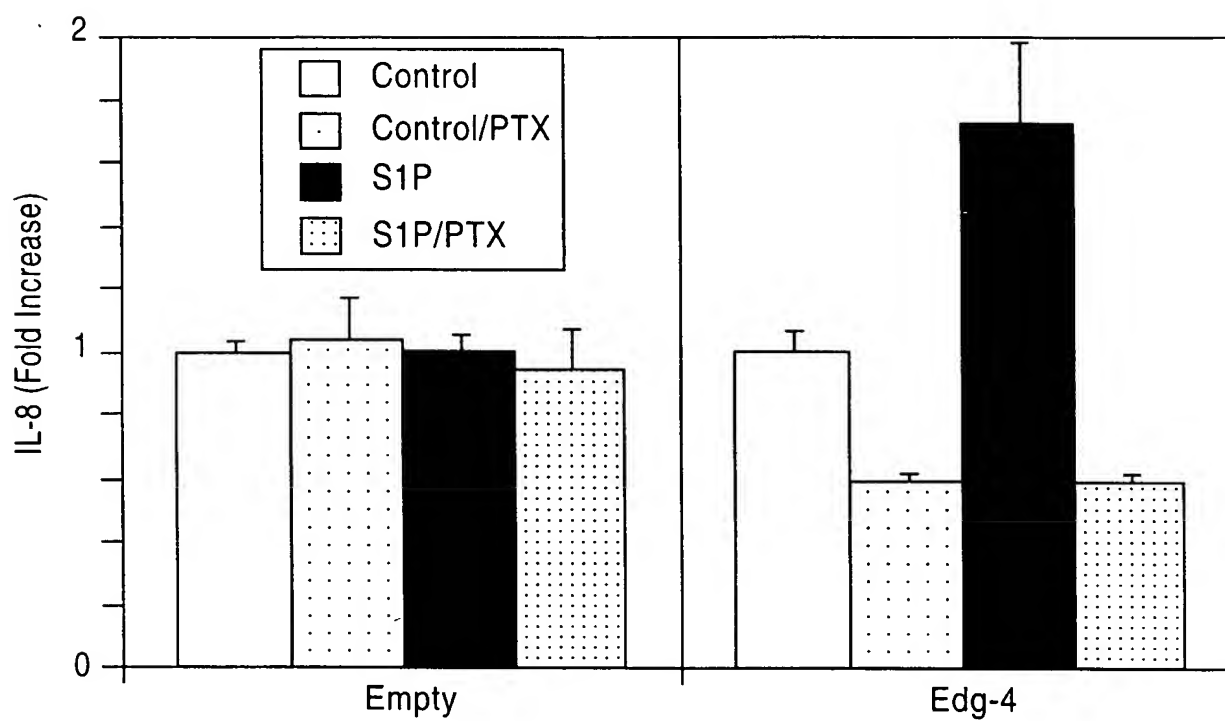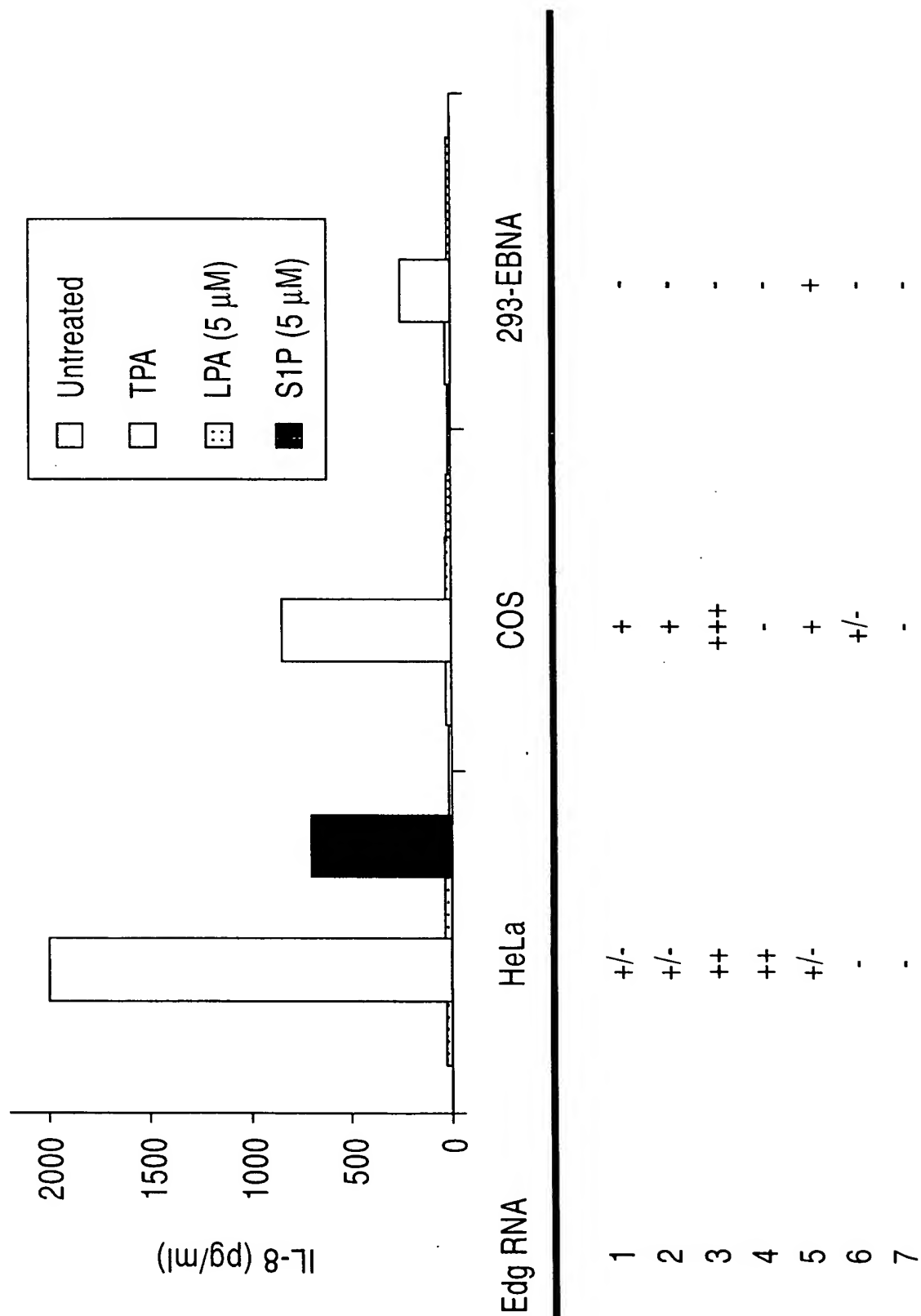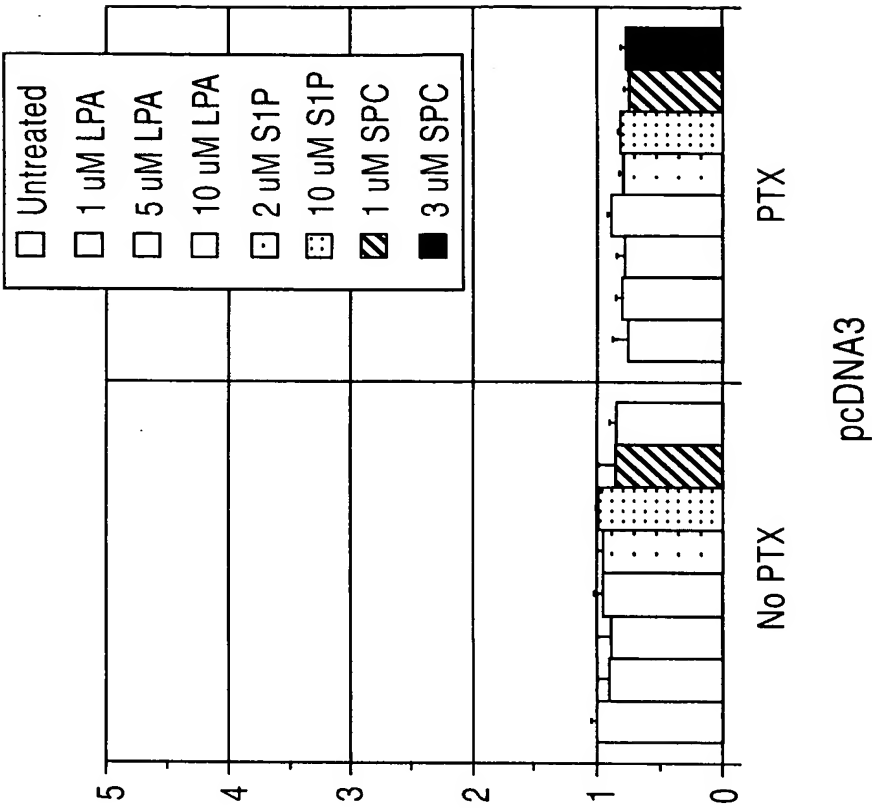
Fig.13A

Fig.13B

Fig.15A-1

```
                                        M   G   S   L   Y   S   E   Y
     AAAGCCCCATGGCCCCAGCAGGCCTCTGAGCCCCACCATGGGCAGCTTGTACTCGGAGTA
  1  ---------+---------+---------+---------+---------+---------+   60
     TTTCGGGGTACCGGGGTCGTCCGGAGACTCGGGGTGGTACCCGTCGAACATGAGCCTCAT

      L   N   P   N   K   V   Q   E   H   Y   N   Y   T   K   E   T   L   E   T   Q
     CCTGAACCCCAACAAGGTCCAGGAACACTATAATTATACCAAGGAGACGCTGGAAACGCA
 61  ---------+---------+---------+---------+---------+---------+   120
     GGACTTGGGGTTGTTCCAGGTCCTTGTGATATTAATATGGTTCCTCTGCGACCTTTGCGT

      E   T   T   S   R   Q   V   A   S   A   F   I   V   I   L   C   C   A   I   V
     GGAGACGACCTCCCGCCAGGTGGCCTCGGCCTTCATCGTCATCCTCTGTTGCGCCATTGT
121  ---------+---------+---------+---------+---------+---------+   180
     CCTCTGCTGGAGGGCGGTCCACCGGAGCCGGAAGTAGCAGTAGGAGACAACGCGGTAACA

      V   E   N   L   L   V   L   I   A   V   A   R   N   S   K   F   H   S   A   M
     GGTGGAAAACCTTCTGGTGCTCATTGCGGTGGCCCGAAACAGCAAGTTCCACTCGGCAAT
181  ---------+---------+---------+---------+---------+---------+   240
     CCACCTTTTGGAAGACCACGAGTAACGCCACCGGGCTTTGTCGTTCAAGGTGAGCCGTTA

      Y   L   F   L   G   N   L   A   A   S   D   L   L   A   G   V   A   F   V   A
     GTACCTGTTTCTGGGCAACCTGGCCGCCTCCGATCTACTGGCAGGCGTGGCCTTCGTAGC
241  ---------+---------+---------+---------+---------+---------+   300
     CATGGACAAAGACCCGTTGGACCGGCGGAGGCTAGATGACCGTCCGCACCGGAAGCATCG

      N   T   L   L   S   G   S   V   T   L   R   L   T   P   V   Q   W   F   A   R
     CAATACCTTGCTCTCTGGCTCTGTCACGCTGAGGCTGACGCCTGTGCAGTGGTTTGCCCG
301  ---------+---------+---------+---------+---------+---------+   360
     GTTATGGAACGAGAGACCGAGACAGTGCGACTCCGACTGCGGACACGTCACCAAACGGGC

      E   G   S   A   F   I   T   L   S   A   S   V   F   S   L   L   A   I   A   I
     GGAGGGCTCTGCCTTCATCACGCTCTCGGCCTCTGTCTTCAGCCTCCTGGCCATCGCCAT
361  ---------+---------+---------+---------+---------+---------+   420
     CCTCCCGAGACGGAAGTAGTGCGAGAGCCGGAGACAGAAGTCGGAGGACCGGTAGCGGTA

      E   R   H   V   A   I   A   K   V   K   L   Y   G   S   D   K   S   C   R   M
     TGAGCGCCACGTGGCCATTGCCAAGGTCAAGCTGTATGGCAGCGACAAGAGCTGCCGCAT
421  ---------+---------+---------+---------+---------+---------+   480
     ACTCGCGGTGCACCGGTAACGGTTCCAGTTCGACATACCGTCGCTGTTCTCGACGGCGTA

      L   L   L   I   G   A   S   W   L   I   S   L   V   L   G   G   L   P   I   L
     GCTTCTGCTCATCGGGGCCTCGTGGCTCATCTCGCTGGTCCTCGGTGGCCTGCCCATCCT
481  ---------+---------+---------+---------+---------+---------+   540
     CGAAGACGAGTAGCCCCGGAGCACCGAGTAGAGCGACCAGGAGCCACCGGACGGGTAGGA

      G   W   N   C   L   G   H   L   E   A   C   S   T   V   L   P   L   Y   A   K
     TGGCTGGAACTGCCTGGGCCACCTCGAGGCCTGCTCCACTGTCCTGCCTCTCTACGCCAA
541  ---------+---------+---------+---------+---------+---------+   600
     ACCGACCTTGACGGACCCGGTGGAGCTCCGGACGAGGTGACAGGACGGAGAGATGCGGTT

      H   Y   V   L   C   V   V   T   I   F   S   I   I   L   L   A   I   V   A   L
     GCATTATGTGCTGTGCGTGGTGACCATCTTCTCCATCATCCTGTTGGCCATCGTGGCCCT
601  ---------+---------+---------+---------+---------+---------+   660
     CGTAATACACGACACGCACCACTGGTAGAAGAGGTAGTAGGACAACCGGTAGCACCGGGA
```
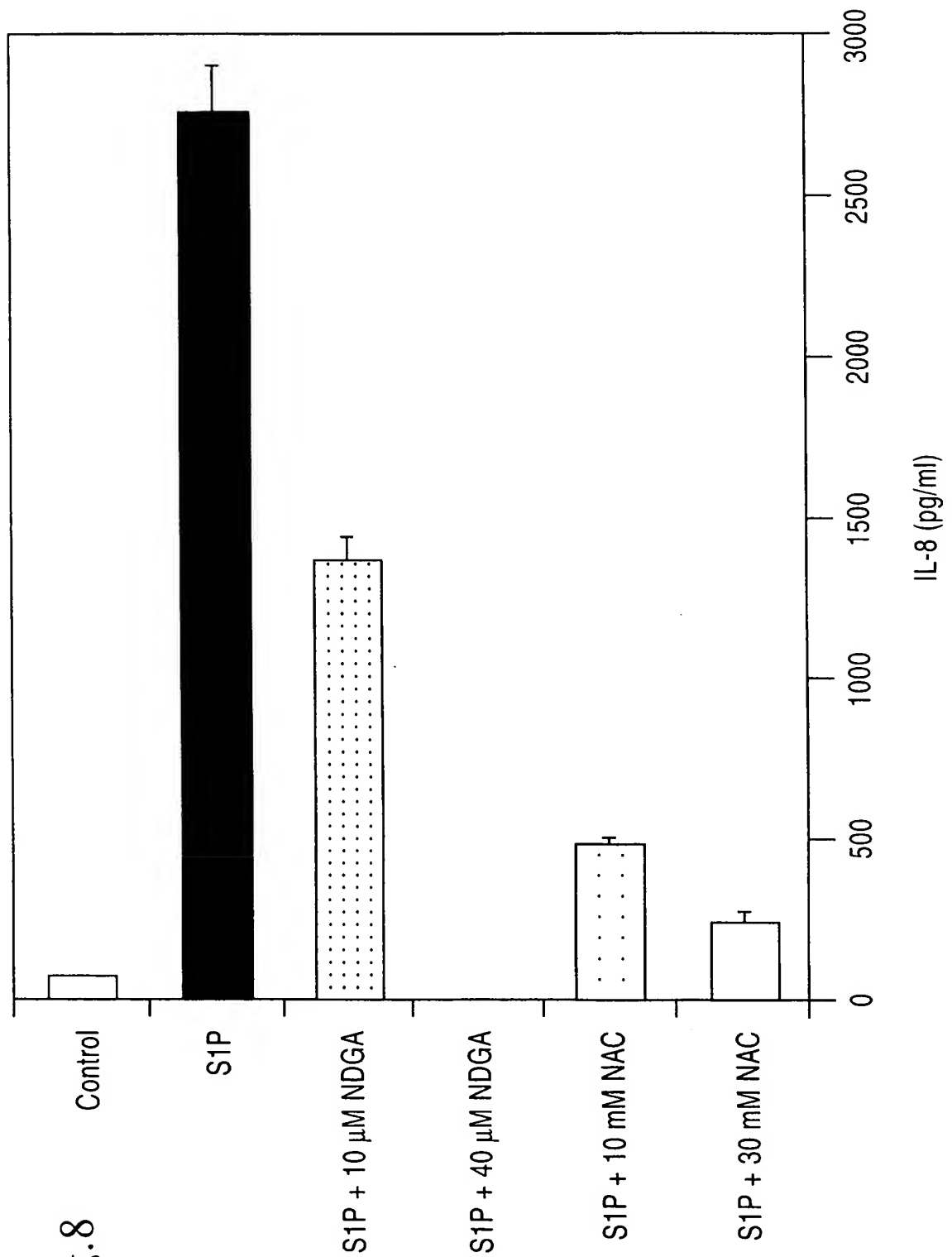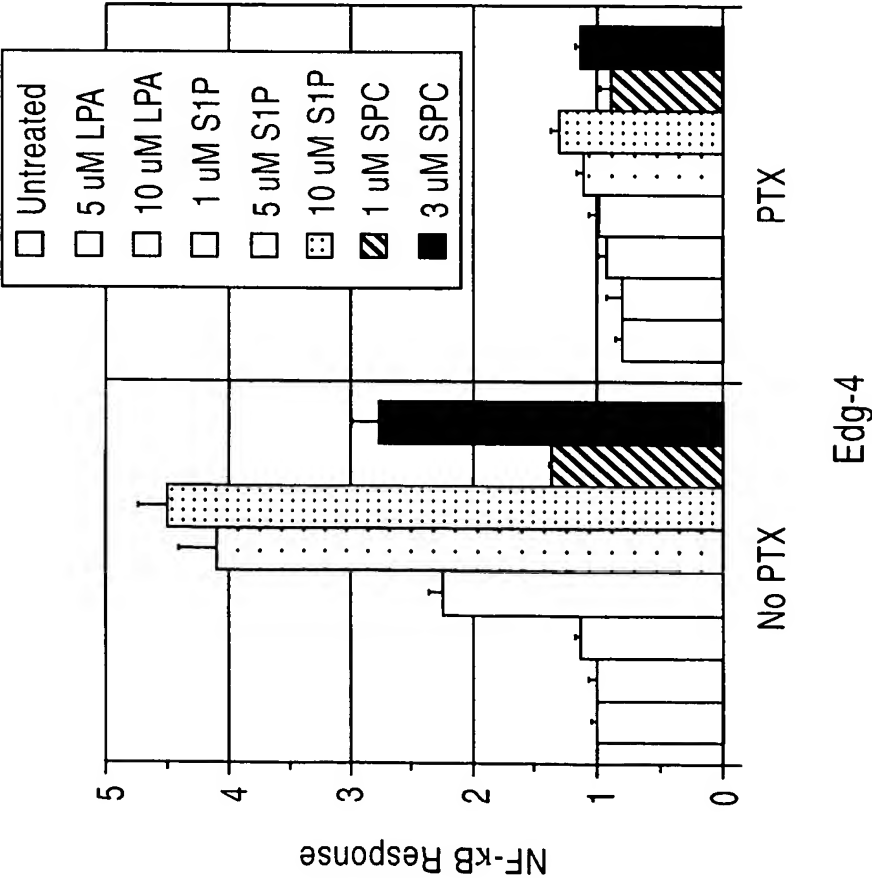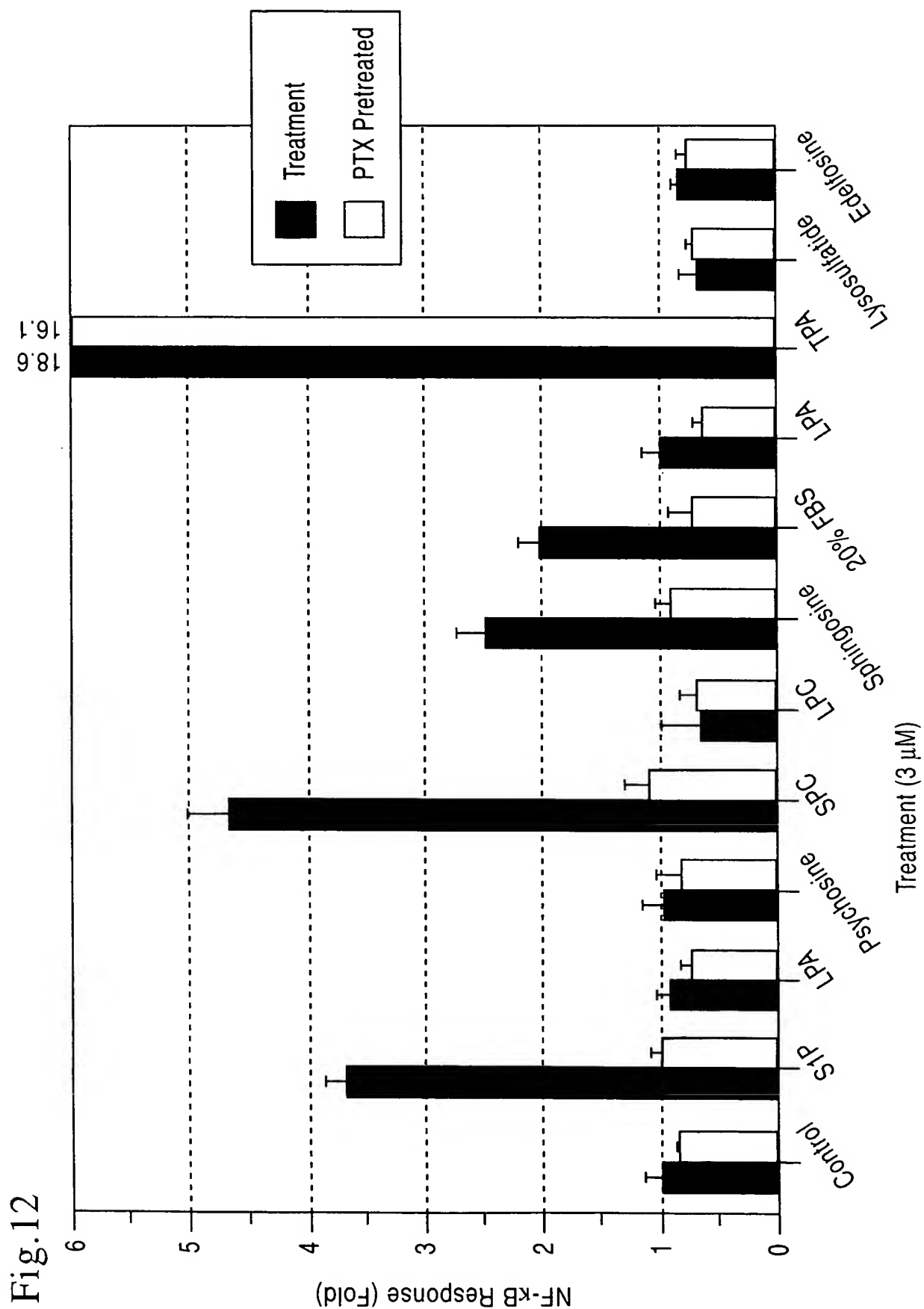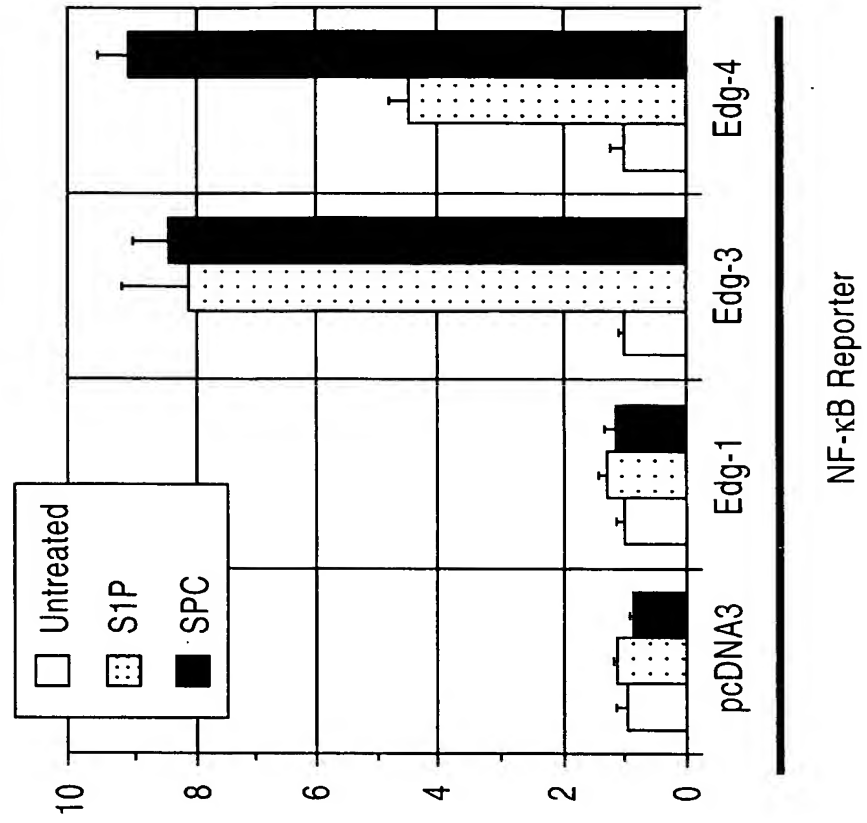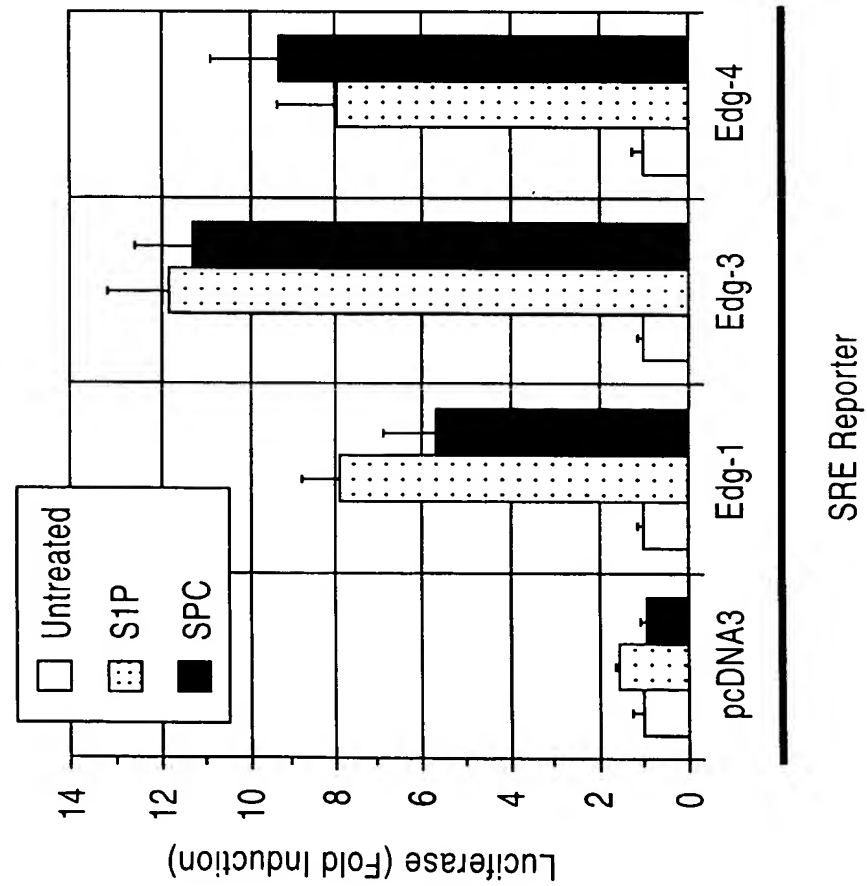
Fig.15A-2

```
        Y   V   R   I   Y   C   V   V   R   S   S   H   A   D   M   A   A   P   Q   T
       GTACGTGCGCATCTACTGCGTGGTCCGCTCAAGCCACGCTGACATGGCCGCCCCGCAGAC
 661   ---------+---------+---------+---------+---------+---------+   720
       CATGCACGCGTAGATGACGCACCAGGCGAGTTCGGTGCGACTGTACCGGCGGGGCGTCTG


        L   A   L   L   K   T   V   T   I   V   L   G   V   F   I   V   C   W   L   P
       GCTAGCCCTGCTCAAGACGGTCACCATCGTGCTAGGCGTCTTTATCGTCTGCTGGCTGCC
 721   ---------+---------+---------+---------+---------+---------+   780
       CGATCGGGACGAGTTCTGCCAGTGGTAGCACGATCCGCAGAAATAGCAGACGACCGACGG


        A   F   S   I   L   L   L   D   Y   A   C   P   V   H   S   C   P   I   L   Y
       CGCCTTCAGCATCCTCCTTCTGGACTATGCCTGTCCCGTCCACTCCTGCCCGATCCTCTA
 781   ---------+---------+---------+---------+---------+---------+   840
       GCGGAAGTCGTAGGAGGAAGACCTGATACGGACAGGGCAGGTGAGGACGGGCTAGGAGAT


        K   A   H   Y   X   F   A   V   S   T   L   N   S   L   L   N   P   V   I   Y
       CAAAGCCCACTACYTTTTCGCCGTCTCCACCCTGAATTCCCTGCTCAACCCCGTCATCTA
 841   ---------+---------+---------+---------+---------+---------+   900
       GTTTCGGGTGATGRAAAAGCGGCAGAGGTGGGACTTAAGGGACGAGTTGGGGCAGTAGAT


        T   W   R   S   R   D   L   R   R   E   V   L   R   P   L   Q   C   W   R   P
       CACGTGGCGCAGCCGGGACCTGCGGCGGGAGGTGCTTCGGCCGCTGCAGTGCTGGCGGCC
 901   ---------+---------+---------+---------+---------+---------+   960
       GTGCACCGCGTCGGCCCTGGACGCCGCCCTCCACGAAGCCGGCGACGTNACGACCGCCGG


        G   V   G   V   Q   G   R   R   R   G   G   T   P   G   H   H   L   L   P   L
       GGGGGTGGGGGTGCAAGGACGGAGGCGGGGCGGGACCCCGGGCCACCACCTCCTGCCACT
 961   ---------+---------+---------+---------+---------+---------+   1020
       CCCCCACCCCCACGTTCCTGCCTCCGCCCCGCCCTGGGGCCCGGTGGTGGAGGACGGTGA


        R   S   S   S   S   L   E   R   G   M   H   M   P   T   S   P   T   F   L   E
       CCGCAGCTCCAGCTCCCTGGAGAGGGGCATGCACATGCCCACGTCACCCACGTTTCTGGA
1021   ---------+---------+---------+---------+---------+---------+   1080
       GGCGTCGAGGTCGAGGGACCTCTCCCCGTACGTGTACGGGTGCAGTGGGTGAAAAGACCT


        G   N   T   V   V   *
       GGGCAACACGGTGGTCTGAGGGTGGGGGTGGACCAACAACCAGGCCAGGGCATAGGGGTT
1081   ---------+---------+---------+---------+---------+---------+   1140
       CCCGTTGTGCCACCAGACTCCCACCCCCACCTGGTTGTTGGTCCGGTCCCGTATCCCCAA


       CATGGAAAGGCCACTGGGTGACCCCAAATA .
1141   ---------+---------+----------+   1170
       GTACCTTTCCGGTGACCCACTGGGGTTTAT
```

Fig.15B-1

cDNA sequence of clone pC3-hedg4#36 encoding functional HEDG4 receptor protein.

```
      ATGGGCAGCTTGTACTCGGAGTACCTGAACCCCAACAAGGTCCAGGAACACTATAATTAT
  1   ---------+---------+---------+---------+---------+---------+   60
      TACCCGTCGAACATGAGCCTCATGGACTTGGGGTTGTTCCAGGTCCTTGTGATATTAATA

      ACCAAGGAGACGCTGGAAACGCAGGAGACGACCTCCCGCCAGGTGGCCTCGGCCTTCATC
 61   ---------+---------+---------+---------+---------+---------+  120
      TGGTTCCTCTGCGACCTTTGCGTCCTCTGCTGGAGGGCGGTCCACCGGAGCCGGAAGTAG

      GTCATCCTCTGTTGCGCCATTGTGGTGGAAAACCTTCTGGTGCTCATTGCGGTGGCCCGA
121   ---------+---------+---------+---------+---------+---------+  180
      CAGTAGGAGACAACGCGGTAACACCACCTTTTGGAAGACCACGAGTAACGCCACCGGGCT

      AACAGCAAGTTCCACTCGGCAATGTACCTGTTTCTGGGCAACCTGGCCGCCTCCGATCTA
181   ---------+---------+---------+---------+---------+---------+  240
      TTGTCGTTCAAGGTGAGCCGTTACATGGACAAAGACCCGTTGGACCGGCGGAGGCTAGAT

      CTGGCAGGCGTGGCCTTCGTAGCCAATACCTTGCTCTCTGGCTCTGTCACGCTGAGGCTG
241   ---------+---------+---------+---------+---------+---------+  300
      GACCGTCCGCACCGGAAGCATCGGTTATGGAACGAGAGACCGAGACAGTGCGACTCCGAC

      ACGCCTGTGCAGTGGTTTGCCCGGGAGGGCTCTGCCTTCATCACGCTCTCGGCCTCTGTC
301   ---------+---------+---------+---------+---------+---------+  360
      TGCGGACACGTCACCAAACGGGCCCTCCCGAGACGGAAGTAGTGCGAGAGCCGGAGACAG

      TTCAGCCTCCTGGCCATCGCCATTGAGCGCCACGTGGCCATTGCCAAGGTCAAGCTGTAT
361   ---------+---------+---------+---------+---------+---------+  420
      AAGTCGGAGGACCGGTAGCGGTAACTCGCGGTGCACCGGTAACGGTTCCAGTTCGACATA

      GGCAGCGACAAGAGCTGCCGCATGCTTCTGCTCATCGGGGCCTCGTGGCTCATCTCGCTG
421   ---------+---------+---------+---------+---------+---------+  480
      CCGTCGCTGTTCTCGACGGCGTACGAAGACGAGTAGCCCCGGAGCACCGAGTAGAGCGAC

      GTCCTCGGTGGCCTGCCCATCCTTGGCTGGAACTGCCTGGGCCACCTCGAGGCCTGCTCC
481   ---------+---------+---------+---------+---------+---------+  540
      CAGGAGCCACCGGACGGGTAGGAACCGACCTTGACGGACCCGGTGGAGCTCCGGACGAGG

      ACTGTCCTGCCTCTCTACGCCAAGCATTATGTGCTGTGCGTGGTGACCATCTTCTCCATC
541   ---------+---------+---------+---------+---------+---------+  600
      TGACAGGACGGAGAGATGCGGTTCGTAATACACGACACGCACCACTGGTAGAAGAGGTAG

      ATCCTGTTGGCCGTCGTGGCCCTGTACGTGCGCATCTACTGCGTGGTCCGCTCAAGCCAC
601   ---------+---------+---------+---------+---------+---------+  660
      TAGGACAACCGGCAGCACCGGGACATGCACGCGTAGATGACGCACCAGGCGAGTTCGGTG

      GCTGACATGGCCGCCCCGCAGACGCTAGCCCTGCTCAAGACGGTCACCATCGTGCTAGGC
661   ---------+---------+---------+---------+---------+---------+  720
      CGACTGTACCGGCGGGGCGTCTGCGATCGGGACGAGTTCTGCCAGTGGTAGCACGATCCG

      GTCTTTATCGTCTGCTGGCTGCCCGCCTTCAGCATCCTCCTTCTGGACTATGCCTGTCCC
721   ---------+---------+---------+---------+---------+---------+  780
```

Fig.15B-2

```
        CAGAAATAGCAGACGACCGACGGGCGGAAGTCGTAGGAGGAAGACCTGATACGGACAGGG

        GTCCACTCCTGCCCGATCCTCTACAAAGCCCACTACCTTTTCGCCGTCTCCACCCTGAAT
781     --------+---------+---------+---------+---------+---------+     840
        CAGGTGAGGACGGGCTAGGAGATGTTTCGGGTGATGGAAAAGCGGCAGAGGTGGGACTTA

        TCCCTGCTCAACCCCGTCATCTACACGTGGCGCAGCCGGGACCTGCGGCGGGAGGTGCTT
841     --------+---------+---------+---------+---------+---------+     900
        AGGGACGAGTTGGGGCAGTAGATGTGCACCGCGTCGGCCCTGGACGCCGCCCTCCACGAA

        CGGCCGCTGCAGTGCTGGCGGCCGGGGGTGGGGGTGCAAGGACGGAGGCGGGGCGGGACC
901     --------+---------+---------+---------+---------+---------+     960
        GCCGGCGACGTCACGACCGCCGGCCCCCACCCCCACGTTCCTGCCTCCGCCCCGCCCTGG

        CCGGGCCACCACCTCCTGCCACTCCGCAGCTCCAGCTCCCTGGAGAGGGGCATGCACATG
961     --------+---------+---------+---------+---------+---------+     1020
        GGCCCGGTGGTGGAGGACGGTGAGGCGTCGAGGTCGAGGGACCTCTCCCCGTACGTGTAC

        CCCACGTCACCCACGTTTCTGGAGGGCAACACGGTGGTCTGA
1021    --------+---------+---------+---------+--     1062
        GGGTGCAGTGGGTGCAAAGACCTCCCGTTGTGCCACCAGACT
```
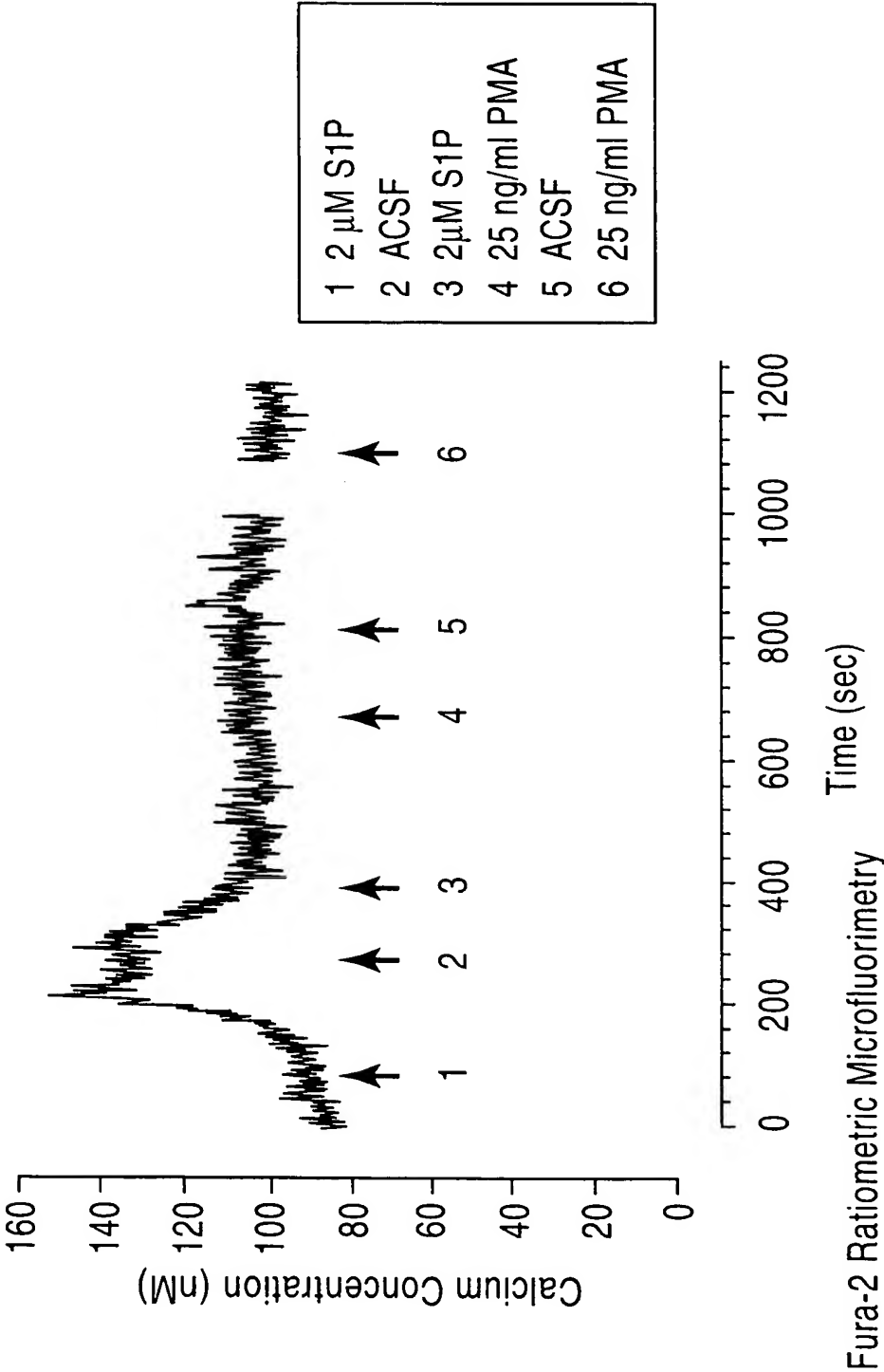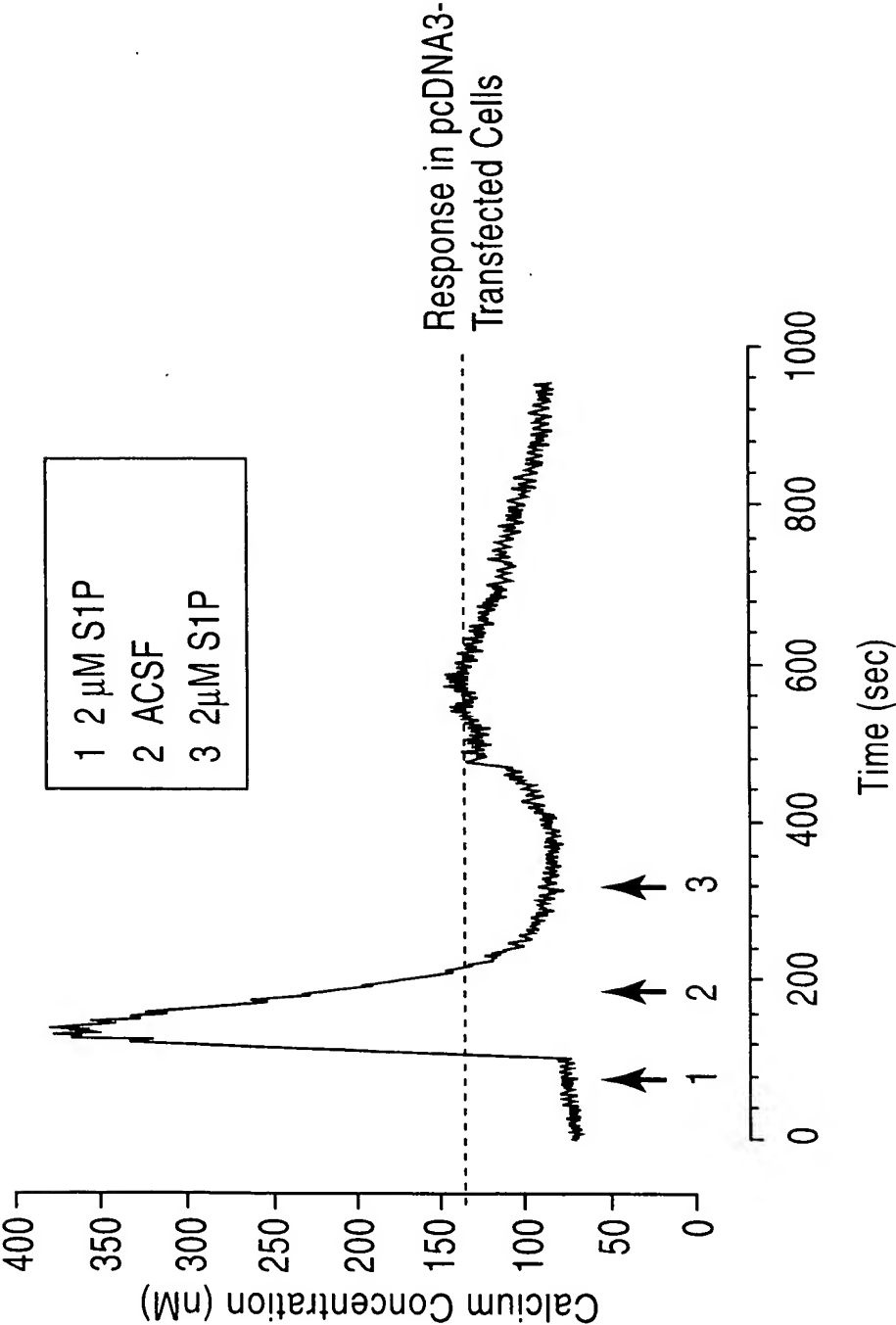
Fig.19

1	2 μM S1P
2	ACSF
3	2μM S1P
4	25 ng/ml PMA
5	ACSF
6	25 ng/ml PMA

Fura-2 Ratiometric Microfluorimetry

Fig.20

Fig.22A

Human Edg-6 Sequence

```
     ATGGTCATCATGGGCCAGTGCTACTACAACGAGACCATCGGCTTCTTCTATAACAACAGT
1    --------+---------+---------+---------+---------+---------+    60
     TACCAGTAGTACCCGGTCACGATGATGTTGCTCTGGTAGCCGAAGAAGATATTGTTGTCA

     GGCAAAGAGCTCAGCTCCCACTGGCGGCCCAAGGATGTGGTCGTGGTGGCACTGGGGCTG
61   --------+---------+---------+---------+---------+---------+    120
     CCGTTTCTCGAGTCGAGGGTGACCGCCGGGTTCCTACACCAGCACCACCGTGACCCCGAC

     ACCGTCAGCGTGCTGGTGCTGCTGACCAATCTGCTGGTCATAGCAGCCATCGCCTCCAAC
121  --------+---------+---------+---------+---------+---------+    180
     TGGCAGTCGCACGACCACGACGACTGGTTAGACGACCAGTATCGTCGGTAGCGGAGGTTG

     CGCCGCTTCCACCAGCCCATCTACTACCTGCTCGGCAATCTGGCCGCGGCTGACCTCTTC
181  --------+---------+---------+---------+---------+---------+    240
     GCGGCGAAGGTGGTCGGGTAGATGATGGACGAGCCGTTAGACCGGCGCCGACTGGAGAAG

     GCGGGCGTGGCCTACCTCTTCCTCATGTTCCACACTGGTCCCCGCACAGCCCGACTTTCA
241  --------+---------+---------+---------+---------+---------+    300
     CGCCCGCACCGGATGGAGAAGGAGTACAAGGTGTGACCAGGGGCGTGTCGGGCTGAAAGT

     CTTGAGGGCTGGTTCCTGCGGCAGGGCTTGCTGGACACAAGCCTCACTGCGTCGGTGGCC
301  --------+---------+---------+---------+---------+---------+    360
     GAACTCCCGACCAAGGACGCCGTCCCGAACGACCTGTGTTCGGAGTGACGCAGCCACCGG

     ACACTGCTGGCCATCGCCGTGGAGCGGCACCGCAGTGTGATGGCCGTGCAGCTGCACAGC
361  --------+---------+---------+---------+---------+---------+    420
     TGTGACGACCGGTAGCGGCACCTCGCCGTGGCGTCACACTACCGGCACGTCGACGTGTCG

     CGCCTGCCCCGTGGCCGCGTGGTCATGCTCATTGTGGGCGTGTGGGTGGCTGCCCTGGGC
421  --------+---------+---------+---------+---------+---------+    480
     GCGGACGGGGCACCGGCGCACCAGTACGAGTAACACCCGCACACCCACCGACGGGACCCG

     CTGGGGCTGCTGCCTGCCCACTCCTGGCACTGCCTCTGTGCCCTGGACCGCTGCTCACGC
481  --------+---------+---------+---------+---------+---------+    540
     GACCCCGACGACGGACGGGTGAGGACCGTGACGGAGACACGGGACCTGGCGACGAGTGCG

     ATGGCACCCCTGCTCAGCCGCTCCTATTTGGCCGTCTGGGCTCTGTCGAGCCTGCTTGTC
541  --------+---------+---------+---------+---------+---------+    600
     TACCGTGGGGACGAGTCGGCGAGGATAAACCGGCAGACCCGAGACAGCTCGGACGAACAG

     TTCCTGCTCATGGTGGCTGTGTACACCCGCATTTTCTTCTACGTGCGGCGGCGAGTGCAG
601  --------+---------+---------+---------+---------+---------+    660
     AAGGACGAGTACCACCGACACATGTGGGCGTAAAAGAAGATGCACGCCGCCGCTCACGTC

     CGCATGGCAGAGCATGTCAGCTGCCACCCCCGCTACCGAGAGACCACGCTCAGCCTGGTC
661  --------+---------+---------+---------+---------+---------+    720
     GCGTACCGTCTCGTACAGTCGACGGTGGGGGCGATGGCTCTCTGGTGCGAGTCGGACCAG

     AAGACTGTTGTCATCATCCTGGGGGCGTTCGTGGTCTGCTGGACACCAGGCCAGGTGGTA
721  --------+---------+---------+---------+---------+---------+    780
     TTCTGACAACAGTAGTAGGACCCCCGCAAGCACCAGACGACCTGTGGTCCGGTCCACCAT

     CTGCTCCTGGATGGTTTAGGCTGTGAGTCCTGCAATGTCCTGGCTGTAGAAAAGTACTTC
781  --------+---------+---------+---------+---------+---------+    840
     GACGAGGACCTACCAAATCCGACACTCAGGACGTTACAGGACCGACATCTTTTCATGAAG
```

Fig.22B

```
     CTACTGcTGGCCGAGGCCAACTCACTGGTCAATGCTGCTGTGTACTCTTGCCGAGATGCT
841  --------+---------+---------+---------+--------+---------+  900
     GATGACgACCGGCTCCGGTTGAGTGACCAGTTACGACGACACATGAGAACGGCTCTACGA

     GAGATGCGCCGCACCTTCCGCCGCCTTCTCTGCTGCGCGTGCCTCCGCCAGTCCACCCGC
901  --------+---------+---------+---------+--------+---------+  960
     CTCTACGCGGCGTGGAAGGCGGCGGAAGAGACGACGCGCACGGAGGCGGTCAGGTGGGCG

     GAGTCTGTCCACTATACATCCTCTGCCCAGGGAGGTGCCAGCACTCGCATCATGCTTCCC
961  --------+----_----+---------+---------+--------+---------+  1020
     CTCAGACAGGTGATATGTAGGAGACGGGTCCCTCCACGGTCGTGAGCGTAGTACGAAGGG

     GAGAACGGCCACCCACTGATGGACTCCACCCTTTAG
1021 --------+---------+---------+------  1056
     CTCTTGCCGGTGGGTGACTACCTGAGGTGGGAAATC
```
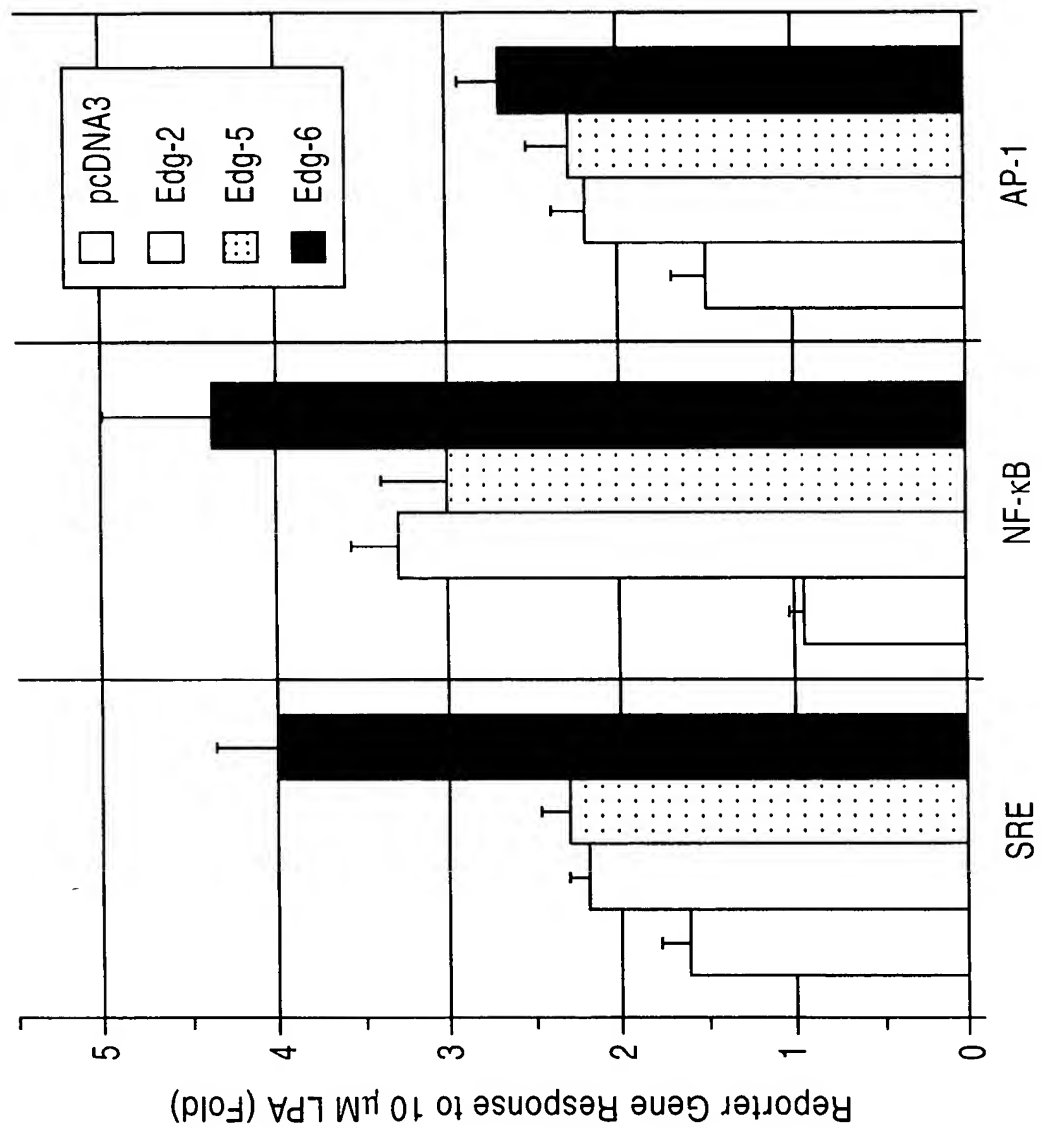
Fig.23

Fig.24
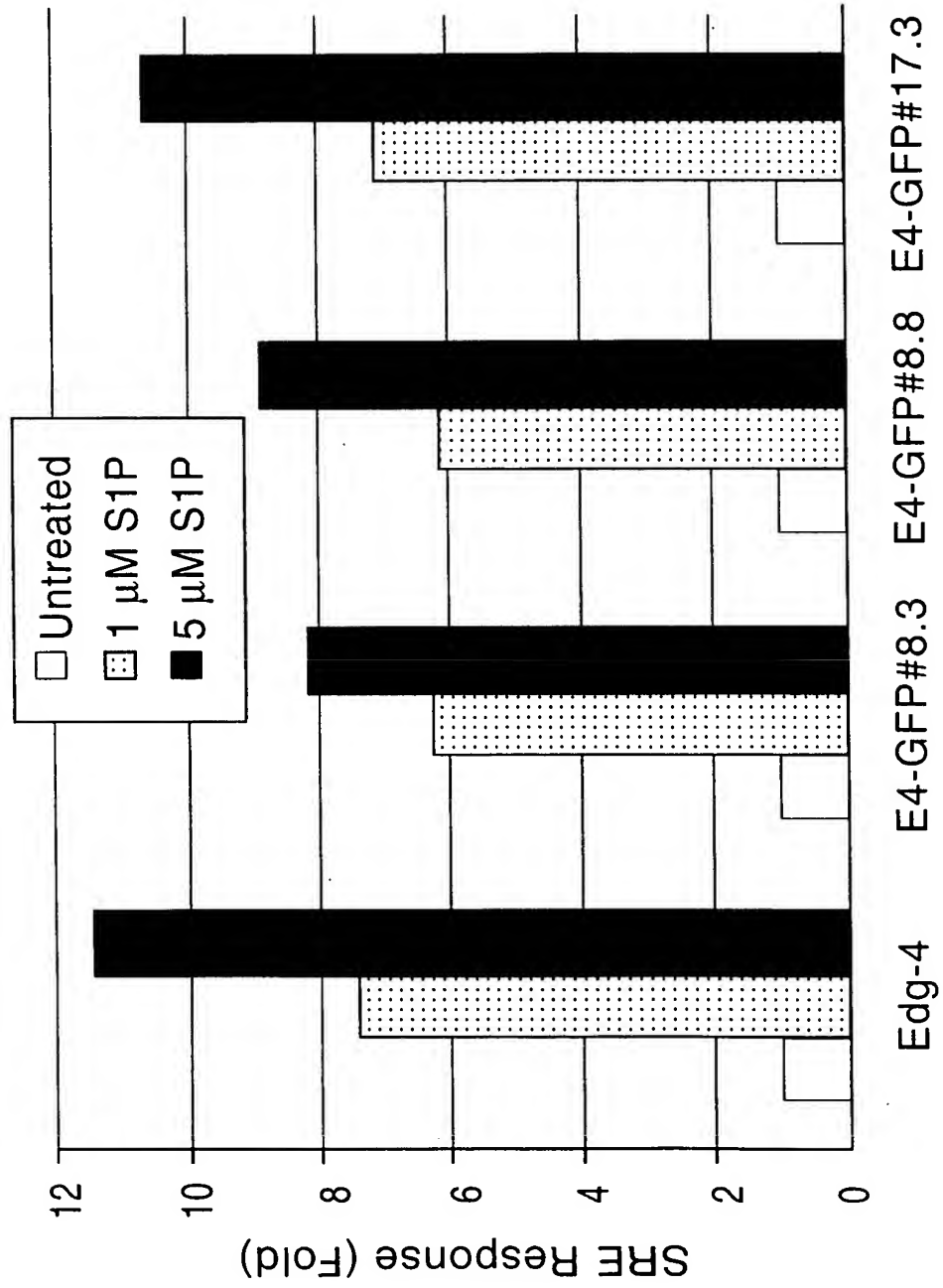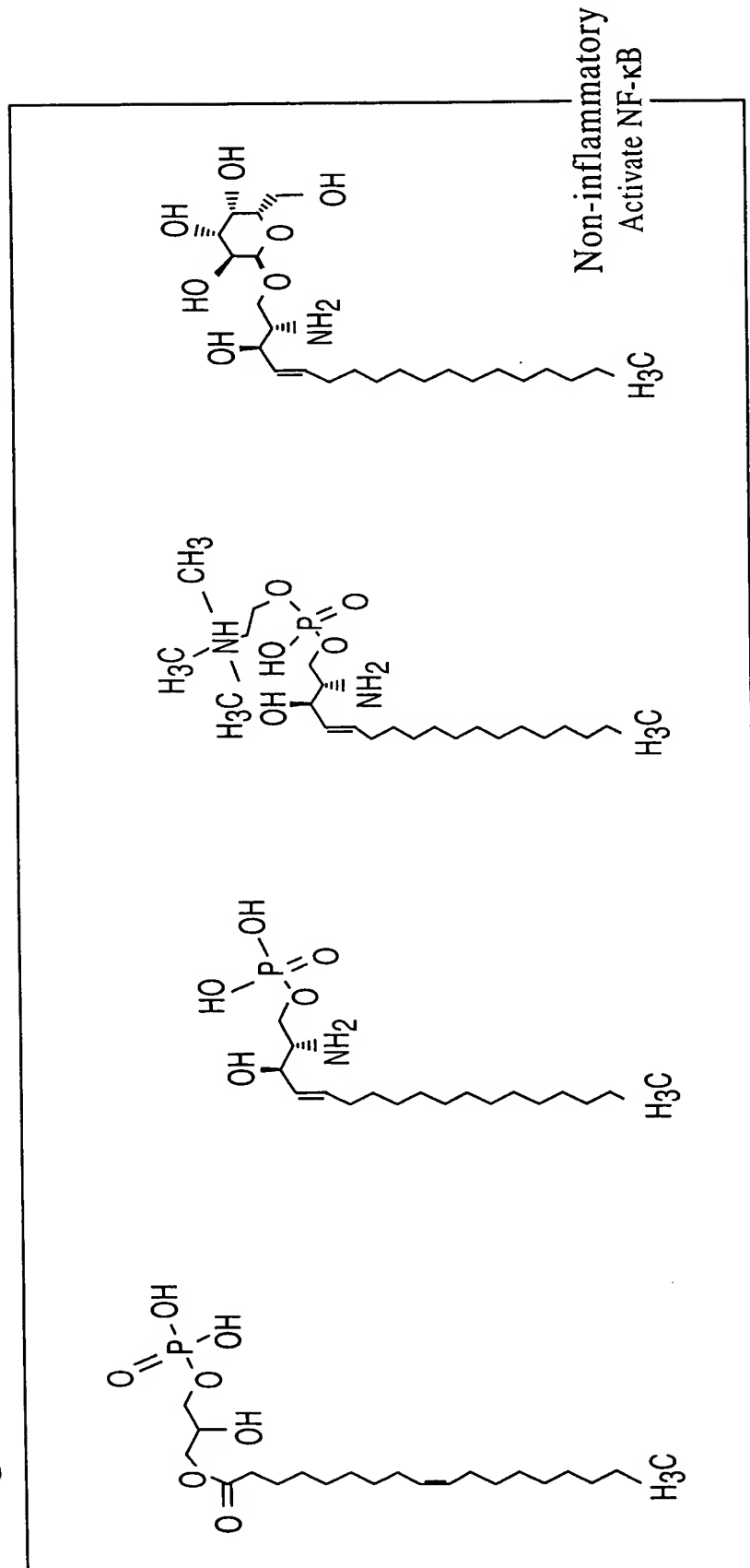
Fig.25

Non-inflammatory
Activate NF-κB

LPA

Edg-2
Edg-5
Edg-6

S1P

Edg-1
Edg-3
Edg-4
Edg-7

SPC

Edg-1
Edg-3
Edg-4
Edg-7

Psychosine

Edg-3
Edg-4